application and further that the Examiner provide Applicants with an initialed copy of the PTO Form 1449 indicating same.

In the Office Action, Claims 1, 2 and 4-8 are rejected under 35 U.S.C. § 102. More specifically, Claims 1, 2 and 4-8 are rejected as allegedly anticipated by *Peritoneal Dialysis International*, Vol. 13, Suppl. 2, October 1992, pp. S116 – S118 ("*Schambye*") in view of U.S. Patent No. 5,296,242 ("*Zander*"); and Claims 1, 2 and 4-8 are rejected as allegedly anticipated by U.S. Patent No. 4,663,166 ("*Veech I*") in view of *Zander*. Applicants respectfully submit that the anticipation rejections are clearly improper.

As a matter of law, "[a]nticipation requires the disclosure in a *single* prior art reference of each element of the claim under consideration." *W.L. Gore and Associates v. Garlock Inc.*, 220 USPQ 303, 313 (Fed. Cir. 1983) *emphasis added*. Indeed, the Court of Appeals for the Federal Circuit has held that "[w]hen more than one reference is required to establish unpatentability of the claimed invention, anticipation under § 102 cannot be found, and validity is determined in terms of § 103. *Continental Can Co. U.S.A. v. Monsanto Co.*, 20 USPQ 2d 1746, 1748 (Fed. Cir. 1991).

In this case, the Patent Office explicitly relies on a secondary reference, namely *Zander*, in support of each of the anticipation rejections. Moreover, the Patent Office rejects the same claims in view of the same references in separate obviousness rejections. This clearly suggests that the Patent Office intended to reject Claims 1, 2 and 4-10 under 35 U.S.C. § 103 and not § 102.

Even if the anticipation rejections are not considered improper as a matter of law, Applicants respectfully submit that the cited references fail to disclose a number of features of the claimed invention. Therefore, Applicants believe that the anticipation rejections are clearly erroneous in law and in fact.

Accordingly, Applicants respectfully request that the anticipation rejections be withdrawn.

In the Office Action, Claims 1-16 are rejected under 35 U.S.C. § 103. More specifically, Claims 1-10 are rejected as allegedly obvious in view of *Schambye* and *Zander*; Claims 1-16 are rejected as allegedly obvious in view of *Veech I* and *Zander*; and Claims 1-16 are rejected as allegedly obvious in view of U.S. Patent No. 6,020,007 ("*Veech II*") and *Zander*. The Patent

Office primarily relies on *Schambye*, *Veech I*, and *Veech II* in support of the obviousness rejections and thus relies on *Zander* to remedy the deficiencies of these references.

Applicants respectfully submit that the obviousness rejections are clearly improper. In general, the claimed invention relates to an improved peritoneal dialysis solution and an improved method of combating metabolic acidosis in peritoneal dialysis patients by administering peritoneal dialysis solutions of the present invention. Of the pending claims, Claims 1, 6, 10 and 11 are the sole independent claims.

As set forth in independent Claim 1, the peritoneal dialysis solution of the present invention includes a bicarbonate concentration of less than or equal to 30 mM/L, a carbon dioxide partial pressure that is less than 60 mmHg and at least one weak acid at a concentration between 15 mEq/L and approximately 20 mEq/L which is selected from the group consisting of lactate, pyruvate, citrate, isocitrate, cis-aconitase, α-ketoglutarate, succinate, fumarate, malate and oxaloacetate. Acetate is not one of the weak acids which is used in the solution of the present invention.

Claims 6 and 10 require the peritoneal dialysis solution to include dextrose, sodium, chloride, calcium, magnesium, bicarbonate in a range from 20.0 to 30.0 mEq/L and a weak acid in a concentration from 10 to 20 mEq/L that is chosen from the group consisting of lactate, pyruvate, citrate, isocitrate, cis-aconitaase, α-ketoglutarate, succinate, fumarate, malate and oxaloacetate. The solution of Claim 6 also has a carbon dioxide partial pressure that is less than 60 mmHg. The solution of Claim 10 has a carbon dioxide partial pressure that is similar to the partial pressure of a normal subject's blood and further has a pH of 7.0 to 7.4.

The method of Claim 11 includes the step of administering to the patient a peritoneal dialysis solution that has a bicarbonate level and a carbon dioxide partial pressure that is substantially similar to that found in the patient's blood and which further includes dextrose, sodium, chloride, calcium, magnesium, bicarbonate in a concentration ranging from 20 to 30 mEq/L and a weak acid in a concentration ranging from 10 to 20 mEq/L.

As previously discussed, the Patent Office primarily relies on *Schambye*, *Veech I*, and *Veech II* in support of its obviousness rejections. Applicants believe that these references fail to disclose or suggest a number of features of the claimed invention. As even admitted by the Patent Office, these references fail to disclose the carbon dioxide partial pressure features of the claimed invention.

In view of same, Applicants believe that the primary references are clearly deficient with respect to the claimed invention. In this regard, the present invention provides a peritoneal dialysis solution that is biochemically balanced to correct metabolic acidosis associated with chronic renal failure in a more physiological manner. The peritoneal dialysis solution of the present invention has a physiological pH and contains bicarbonate at a concentration that is found in blood involved in diffusive transport of solutes with dialysis fluid. This will block the loss of bicarbonate during peritoneal dialysis, which is the case with known solutions. Additionally, the solution contains carbon dioxide at a partial pressure that is similar to a partial pressure of carbon dioxide found in the blood capillaries. The peritoneal dialysis solution also contains a weak acid at a specified amount needed to neutralize acid generated from endogenus metabolism. These weak acids are also the normal biochemical intermediates of glucose metabolism resulting in neutral end products. See, Specification, page 4, lines 7-24. Therefore, Applicants believe that, at a minimum, nowhere do these references disclose or suggest the carbon dioxide partial pressure features, let alone the carbon dioxide partial pressure features combined with the additional other features, such as the unique combination of two buffers(bicarbonate and a weak acid), to provide a biochemically balanced peritoneal dialysis solution capable of correcting metabolic acidosis as required by the claimed invention.

Further, Applicants do not believe that the Patent Office can rely solely on *Zander* to remedy the deficiencies of the primary references. While *Zander* does teach a dialysis solution with a carbon dioxide partial pressure of about 40 mmHg, a person skilled in the art of peritoneal dialysis would readily recognize that the solutions proposed by *Zander* would not be effective in maintaining the acid-base balance of dialysis patients.

Specifically, the "preliminary research" disclosed in *Zander* at column 2, lines 35-39, discloses a solution having a bicarbonate concentration and carbon dioxide partial pressure corresponding to physiological blood plasma values. However, column 2 of the *Zander* reference does not disclose the weak acid that is necessary as a second buffer because of the relatively low concentration of bicarbonate. Contrary to the Patent Office's position, the preferred weak acid of *Zander* clearly is acetic acid/acetate at a concentration of 27.2 mmole/L in the combined solution. Indeed, *Zander* discloses a solution can be used with advantage as a dialysis, substitution or infusion solution at this acetic acid/acetate concentration. See, *Zander*, col. 6, lines 51-52.

The use of acetate in this high concentration has at least two problems. First, it has been known for over 10 years that acetate damages the peritoneal membrane causing loss of ultrafiltration. See Faller and Marichal, "Loss of Ultrafiltration and Continuous Ambulatory Peritoneal Dialysis: A Role for Acetate," *Peritoneal Dialysis Bulletin*, Jan.-Mar. 1984 (Exhibit A of Applicants' Amendment dated April 30, 2002).

Further, the acetate concentration (e.g., 27.2 mmole/L) is too high. To support this position, Applicants have submitted the Declaration of Dr. Martis in the parent application and also attached as Exhibit B to Applicants' Amendment mailed on April 30, 2002. As set forth therein, by utilizing a weak acid concentration that is too high (e.g., 27.2 mmole/L), *Zander* teaches a solution that is incapable of maintaining a proper acid-base balance. Hence, because *Zander* fails to disclose a solution with a buffer content capable of maintaining the acid-base balance and because *Zander* promotes the use of acetate, one skilled in the art would not look to *Zander* for guidance in designing a peritoneal dialysis solution as required by the claimed invention contrary to the Patent Office's position.

Indeed, the present invention provides a unique combination of two buffers (bicarbonate and a weak acid, such as selected from a group that does not include acetic acid) which is both safe and effective as previously discussed. The safety and the efficacy of the solution of the present invention is established by the data presented in the Declaration of Dr. Martis. In view of same, Applicants believe that one skilled in the art of peritoneal dialysis would readily recognize that the solution proposed by *Zander* will lead to metabolic alkalosis and therefore is not suitable for use as a dialyzing fluid for long term maintenance dialysis.

Further, nowhere does *Zander* disclose or suggest the ratio of the two buffers used in the present invention. For example, Applicants believe that one skilled in the art viewing *Zander* would not be inclined to use the type and/or amount of weak acid as required by the claimed invention. Contrary to the Patent Office's position, the clear emphasis of *Zander* is to use acetic acid/acetate at a concentration of 27.2 mmole/l. See, *Zander*, col. 6, lines 47-52. As noted above, this weak acid concentration clearly falls outside the scope of the claimed invention. Further, independent Claims 1, 6 and 10 relate to peritoneal dialysis solutions without acetic acid. Moreover, as noted in the Declaration of Dr. Martis, acetate damages the peritoneal membrane causing loss of ultrafiltration. Therefore, *Zander*, with its high acetate concentration that exceeds

the weak acid limit required by the claimed invention, clearly teaches away from the claimed solution.

In view of same, Applicants do not believe that one skilled in the art would be inclined to modify any one or all of the primary references with the alleged teachings of *Zander* to arrive at the claimed invention. What the Patent Office clearly has done is to simply piece together the cited references by selectively picking and choosing teachings of each of the references in an attempt to explain what the claimed invention discloses. Of course, the Court of Appeals for the Federal Circuit has criticized this motivation to combine analysis as being "hindsight reconstructive" because the motivation to combine the references was first disclosed in the present invention. *In re O'Farrell,* 853 F.2d., 894, 902-903 (Fed. Cir. 1988).

Moreover, one skilled in the art might find it "obvious to try" the peritoneal dialysis solutions of the claimed invention by, for example, providing a peritoneal dialysis solution with a combination of two buffers, namely bicarbonate and a weak acid, in addition to a carbon dioxide partial pressure at specified amounts such that the peritoneal dialysis solution can be effectively utilized to correct for metabolic acidosis when administered to a patient as required by the claimed invention. However, an "obvious to try" analysis is not the proper standard under 35 U.S.C. §103. *In re Geiger,* 2 U.S.P.Q. 2d 1276, 1278 (Fed. Cir. 1987). An "obvious to try" test would often deny patent protection to inventions growing out of well-planned research which is, of course, guided into those areas in which success is deemed most likely. *In re Lindell,* 155 U.S.P.Q. 521, 523 (C.C.P.A. 1967).

As previously discussed, Applicants have discovered peritoneal dialysis solutions with a specific make-up such that the solutions can be effectively utilized to correct for metabolic acidosis when administered to a patient suffering or likely to suffer from same as required by the claimed invention. Nowhere do any of the cited references recognize such beneficial effects of the claimed invention.

As previously discussed, the primary references are clearly deficient at least with respect to the carbon dioxide partial pressure features of the claimed invention. Further, the Patent Office relies solely on *Zander* to remedy the deficiencies of the primary references. But, *Zander* clearly fails to disclose or suggest to the extent that it effectively teaches away from a peritoneal dialysis solution that combines bicarbonate, a weak acid and carbon dioxide at the specific concentration levels as required by the claimed invention. Indeed, the Court of Appeals for the

Federal Circuit has held "there is no suggestion to combine...if a reference [e.g., *Zander*] teaches away from its combination with another source." *Tec Air, Inc. v. Denso Manufacturing Michigan Inc.*, 52 U.S.P.Q. 2d 1294 (Fed. Cir. 1999).

In this regard, *Zander* clearly discloses the use of an acetic acid/acetate concentration that is too high for purposes of maintaining a proper acid-base balance as previously discussed. Why then would one skilled in the art be inclined to modify the solutions disclosed in the primary references with what Zander discloses to arrive at the claimed invention? Therefore, the Patent Office has improperly combined the cited references. Moreover, Appellants respectfully submit that, even if combinable, the references fail to disclose or suggest a number of features of the claimed invention. Therefore, the cited art fails to render obvious the claimed invention.

Accordingly, Applicants respectfully request that the obviousness rejections be withdrawn.

For the foregoing reasons, Applicants respectfully request reconsideration of the patent application and earnestly solicit an early allowance of same.

Respectfully submitted,

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